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Human Papillomavirus and Cardiovascular Disease Among U.S. Women in the National Health and Nutrition Examination Survey, 2003 to 2006

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Objectives The purpose of this study was to examine the association between human papillomavirus (HPV) and cardiovascular disease (CVD) among U.S. women.

Background Oncogenic proteins derived from tumor-associated HPV induce the degradation of tumor suppressor protein p53. Inactivation of p53 is associated with accelerated atherosclerotic process. However, the association between HPV infection with CVD remains unclear.

Methods Data were from 2,450 women (age 20 to 59 years) in the National Health and Nutrition Examination Survey, 2003 to 2006. Self-collected vaginal swab specimens were sent for HPV DNA analysis by L1 consensus polymerase chain reaction followed by type-specific hybridization. CVD was ascertained by self-reported diagnosis of myocardial infarction or stroke.

Results A total of 60 females (39 women were HPV DNA positive, whereas 21 were negative) had coronary artery disease. Presence of vaginal HPV DNA was associated with CVD. Odds ratio (OR) of CVD comparing women with presence of vaginal HPV DNA to those without was 2.30 (95% confidence interval [CI]: 1.27 to 4.16) after controlling for demographics, health/sex behaviors, medical comorbidities, cardiovascular risk factors, and management. At the same level of adjustment, OR of CVD comparing women with cancer-associated HPV types to those with negative HPV was 2.86 (95% CI: 1.43 to 5.70).

Conclusions HPV infection, especially cancer-associated oncogenic types, is associated with CVD among women. (J Am Coll Cardiol 2011;58:2001–6) © 2011 by the American College of Cardiology Foundation

Extensive research indicates that cigarette smoking, diabetes, dyslipidemia, and hypertension, collectively labeled as conventional risk factors, are important contributors to cardiovascular disease (CVD) (1–3) and that treatment of these risk factors is associated with reduced risk of future cardiovascular events (4). However, nearly 20% of individuals with CVD do not have any of the conventional risk factors (5), indicating that other "nontraditional" factors may play an essential role in the development of CVD.

Human papillomavirus (HPV) infection is one of the most common sexually transmitted infections in the United States. A recent study from the National Health and Nutrition Examination Survey (NHANES) reported an overall HPV prevalence of 26.8% (6). HPVs, especially "oncogenic" or cancer-associated types, are implicated as a causative agent of anogenital cancers (7,8). The viral oncoproteins bind to cellular tumor-suppressor protein p53 and therefore induce the degradation of p53 through the ubiquitin pathway (9,10). p53 is essential in regulating the process of atherosclerosis (11). Absence of p53 has been shown to accelerate atherosclerosis in vivo (12), and human

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study also demonstrated an association between p53 inactivation and post-atherectomy coronary restenosis (13). Although the role of HPV is well known in the development of anogenital cancers, the potential atherosclerotic outcome of HPV infection (through interaction between HPV oncoproteins and p53) is largely unknown and has not been investigated. We hypothesized that HPV infection is associated with CVD among women. The objective of this study was to test the hypothesis by analyzing data from the NHANES 2003 to 2006.

Methods

Data source and study sample. The data come from the NHANES 2003 to 2006, a population-based cross-sectional

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Abbreviations and Acronyms

BP = blood pressure
CI = confidence interval
CVD = cardiovascular disease
HDL = high-density lipoprotein
HPV = human papillomavirus
OR = odds ratio
STD = sexually transmitted disease

survey designed to collect information on the health and nutrition of the U.S. civilian noninstitutionalized population.

Of 3,467 females aged 20 to 59 years who were interviewed at home for the 2003 to 2006 cycles, 3,330 were examined in a mobile examination center. Among them, 2,829 females (85.0%) submitted cervicovaginal swab specimens, whereas 501 females did not. Of the 2,829 females who submitted cervicovaginal swab specimens, 42 females submitted an inadequate swab specimen. A total of 543 females (16.3%) were considered nonresponders because they either submitted an inadequate swab specimen (n = 42) or they did not submit a swab specimen (n = 501). Compared with responders, nonresponders were significantly more likely to be of all other race (race/ethnicity other than Hispanic, black, or white) (8.8% vs. 4.4%, $p < 0.001$), and to be younger (age 34.0 years vs. 37.7 years, $p < 0.001$). Among the 2,787 women with adequate specimens, we further excluded 337 participants with missing covariates in laboratory measurements or health behavior questionnaire, leaving 2,450 women as the final analytic sample.

HPV DNA examination and genotyping. Self-collected vaginal swabs were evaluated for HPV infection. Vaginal specimens were processed, stored, and then shipped to Atlanta, Georgia, for analysis. DNA was extracted using modifications of QIAmp Mini Kit protocol (Qiagen, Valencia, California) within 1 month of sample collection, and HPV detection and genotyping were conducted as described elsewhere (6). In brief, HPV detection and typing were performed by using the Roche Linear Array Assay (Roche Molecular Systems Inc, Pleasanton, California). The assay used HPV L1 consensus polymerase chain reaction (PCR) with biotinylated PGMY09/11 primer sets and β -globin as an internal control for sample amplification. The primer mix amplifies essentially all HPV types found in the genital tract. After amplification, the samples were then typed by hybridization to the typing strips followed by colorimetric detection. The strip was a linear array of probes specific for 37 HPV types (6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, IS39, and 89) and for positive β-globin as well. Types were read by comparing the reaction pattern to the typing template. Samples negative for both β-globin and HPV were considered inadequate for interpretation (n = 42, 1.48%) and were omitted from further analysis. HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 were defined as oncogenic or cancer-associated HPV types (14).

Cardiovascular disease. Cardiovascular disease (CVD) was ascertained by self-reported questionnaires: "Has a doctor or other health professional ever told you that you had a heart attack (also called myocardial infarction)?" or "Has a doctor or other health professional ever told you that you had a stroke?" Answering yes to either question was coded positive for CVD.

Assessment of demographics and clinical factors. Age, race, sex behavior, and alcohol consumption were obtained by self-report. Sex was defined as vaginal, oral, or anal sex. Body mass index, calculated as weight in kilograms divided by the square of height in meters, was categorized according to the National Institutes of Health obesity standards: <18.5 = underweight, 18.5 to 24.9 = normal weight, 25.0 to 29.9 = overweight, and >30 = obese (15). Using their serum cotinine concentrations, we classified smoking status of participants into 4 groups: nonsmoker (<14 ng/ml), light smoker (14 to 99 ng/ml), moderate smoker (100 to 199 ng/ml), and heavy smoker (>200 ng/ml) (16). Comorbidities, including lung disease (defined as asthma, emphysema, or chronic bronchitis), liver disease, thyroid disease, sexually transmitted diseases (STDs), or cancer (including cervical cancer or all other cancer), use of cholesterol-lowering medications, and use of antihypertensive medications, were ascertained by self-report. Diabetes was defined by self-report of a physician's diagnosis, the presence of a fasting (fasting >6 h) plasma glucose level >126 mg/dl or a nonfasting (fasting <6 h) glucose level > 200 mg/dl, hemoglobin A_{1C} ≥6.5% (5), or the use of diabetic medications. Hypertension was defined as mean systolic blood pressure (BP) >140 mm Hg, mean diastolic BP >90 mm Hg, physician diagnosis, or use of antihypertensive medications. Mean BP was composed of up to 4 readings on 2 separate occasions. Waist circumference was measured at the iliac crest to the nearest 0.1 cm. Serum triglycerides, high-density lipoprotein (HDL) cholesterol, C-reactive protein, serum creatinine, urinary albumin, urinary creatinine were analyzed by laboratory methods reported elsewhere (17,18). Urinary albumin-to-creatinine ratio (in milligrams per gram) was calculated accordingly. Estimated glomerular filtration rate was calculated by using the Modification of Diet in Renal Disease study equation (19).

Analysis. Demographic and clinical characteristics of the study population were presented according to HPV genotypes, namely, cancer-associated HPV types (n = 573), other HPV types (n = 568), or negative HPV (n = 1,309). Chi-square test or *t*-test was used to determine differences between groups. Association of metabolic risks with HPV genotypes was examined using multiple regression. To consider various metabolic risk factors as a whole, we also calculated the metabolic *z*-score. The score was derived by converting each component of the metabolic risk factors, namely blood pressure, waist circumference, levels of glucose, triglyceride level, and HDL level, into a *z*-score based on means of the study population (20). The metabolic *z*-score was calculated by summation of the former 4 *z*-scores minus the HDL *z*-score. Multiple logistic regression analysis was used to examine the association of HPV

DNA, HPV genotypes, and CVD. Women with negative HPV DNA were the reference category. We used an extended-model approach for covariate adjustment: Model 1 = age and race; Model 2 = Model 1 + health behaviors (smoking and alcohol consumption) and sex behavior; Model 3 = Model 2 + medical comorbidities (lung disease, liver disease, thyroid disease, estimated glomerular filtration, STDs, history of cervical cancer, history of all other cancer); Model 4 = Model 3 + cardiovascular risk factors and management (hypertension, diabetes mellitus, waist circumference, triglycerides, HDL cholesterol, log-transformed levels of C-reactive protein and urinary albumin-to-creatinine ratio, use of antihypertensive agents or cholesterol-lowering medications); and Model 5 = Model 3 + metabolic *z*-score, use of antihypertensive agents or cholesterol-lowering medications.

NHANES weights were not adjusted in the analyses because they apply to prevalence estimates of the entire population, and our study aimed to evaluate associations in a certain subset of women with valid data of HPV DNA examination and genotyping. Data analyses were performed using STATA 10.0 software (STATA Corporation, College Station, Texas).

Results

Women in this study were generally young, with a mean age of 37.9 years. The prevalence of CVD was low, with a total of 60 women (2.5%) reported having either myocardial infarction or stroke. Among study participants (N = 2,450), 1,141 women (46.6%) were positive for HPV DNA. Five hundred seventy-three women (23.2% of study population) had cancer-associated HPV types. Characteristics of the study sample by HPV genotypes were summarized (Table 1). Women without HPV infection tended to be nonsmokers and to drink less, whereas women with cancer-associated HPV types were more likely to be younger and tended to have higher prevalence of CVD. There was no difference in prevalence of diabetes mellitus, lung disease, liver disease, thyroid disease, and cancer between groups.

Association between HPV and various metabolic risks. Various metabolic risks, including systolic blood pressure, diastolic blood pressure, abdominal circumference, levels of blood glucose, triglyceride, and HDL cholesterol, and a composite metabolic *z*-score were compared in 3 different groups: cancer-associated HPV types, other HPV types, and negative HPV. We did not find any association between HPV and various metabolic risks. Adjusted means of various metabolic risks were comparable across 3 different groups after controlling for age, race, and health/sex behaviors (Table 2).

Association between HPV and cardiovascular disease. The results of multiple logistic regression analysis for the association between HPV and CVD are summarized in Table 2. After adjusting for age and race, presence of vaginal HPV DNA was associated with CVD. Odds ratio (OR) of

Table 1 Characteristics of Study Participants According to HPV Genotypes, NHANES 2003 to 2006 (N = 2,450)

Variables	HPV Genotype			Total (N = 2,450)	p Value
	Cancer-Associated HPV Types (n = 573)	Other HPV Types (n = 568)	Negative (n = 1,309)		
Age group					<0.001
20–29 yrs	218 (38.0)	141 (24.8)	355 (27.1)	714 (29.2)	
30–45 yrs	209 (36.5)	255 (44.9)	546 (41.7)	1,010 (41.2)	
46–59 yrs	146 (25.5)	172 (30.3)	408 (31.2)	726 (29.6)	
Race					<0.001
Mexican American	113 (19.7)	114 (20.1)	279 (21.3)	506 (20.7)	
Other Hispanics	18 (3.2)	22 (3.9)	49 (3.7)	89 (3.6)	
Non-Hispanic white	254 (44.3)	242 (42.6)	691 (52.8)	1,187 (48.4)	
Non-Hispanic black	166 (29.0)	170 (29.9)	222 (17.0)	558 (22.8)	
All others	22 (3.8)	20 (3.5)	68 (5.2)	1,10 (4.5)	
≥12 alcoholic drinks in the last yr	382 (66.7)	363 (63.9)	785 (60.0)	1,530 (62.5)	0.016
Nonsmoker	395 (68.9)	415 (73.1)	1,078 (82.4)	1,888 (77.1)	<0.001
Ever had sex behavior	548 (95.6)	540 (95.1)	1,219 (93.1)	2,307 (94.2)	0.058
Cardiovascular disease	20 (3.5)	19 (3.35)	21 (1.6)	60 (2.5)	0.015
Hypertension	124 (21.6)	161 (28.4)	289 (22.1)	574 (23.5)	0.007
Diabetes mellitus	38 (6.6)	42 (7.4)	95 (7.3)	175 (7.1)	0.858
Lung disease	119 (20.8)	124 (21.8)	240 (18.3)	483 (19.7)	0.167
Liver disease	15 (2.6)	18 (3.2)	30 (2.3)	63 (2.6)	0.543
Thyroid disease	68 (11.9)	60 (10.6)	154 (11.8)	282 (11.5)	0.721
Cancer	33 (5.8)	28 (4.9)	68 (5.2)	129 (5.3)	0.810
Cervical cancer	12 (2.1)	10 (1.8)	22 (1.7)	44 (1.8)	0.822
All other cancer	21 (3.7)	18 (3.2)	46 (3.5)	85 (3.5)	0.893
Sexually transmitted disease	84 (14.7)	86 (15.1)	107 (8.2)	277 (11.3)	<0.001

Cancer-associated human papillomavirus (HPV) types = HPV types 16, 18, 31, 33, 35, 39, 45 51, 52, 56, 58, 59, and 68.

Table 2 Relation of HPV to Various Metabolic Risks

Metabolic Risks	HPV Genotypes	β*(Standard Error)	p Value	Adjusted Means†
Systolic blood pressure, mm Hg	HPV negative	Reference		115.2
	Other HPV types	0.92 (0.74)	0.214	116.2
	Cancer-associated HPV types	0.62 (0.75)	0.404	115.9
Diastolic blood pressure, mm Hg	HPV negative	Reference		68.7
	Other HPV types	0.95 (0.55)	0.084	69.7
	Cancer-associated HPV types	−0.34 (0.55)	0.539	68.4
Abdominal circumference, cm	HPV negative	Reference		95.0
	Other HPV types	0.56 (0.81)	0.494	95.5
	Cancer-associated HPV types	0.53 (0.82)	0.513	95.5
Blood glucose, mg/dl	HPV negative	Reference		92.9
	Other HPV types	−1.43 (1.31)	0.275	91.4
	Cancer-associated HPV types	−1.12 (1.32)	0.396	91.7
Triglyceride, mg/dl	HPV negative	Reference		131.4
	Other HPV types	−5.50 (7.93)	0.488	125.9
	Cancer-associated HPV types	−2.04 (8.01)	0.799	129.4
HDL cholesterol, mg/dl	HPV negative	Reference		60.2
	Other HPV types	−0.42 (0.85)	0.617	59.8
	Cancer-associated HPV types	−0.09 (0.85)	0.912	60.2
Metabolic *z*-score	HPV negative	Reference		−0.054
	Other HPV types	0.05 (0.14)	0.729	−0.006
	Cancer-associated HPV types	0.02 (0.14)	0.898	−0.036

Cancer-associated HPV types = HPV types 16, 18, 31, 33, 35, 39, 45 51, 52, 56, 58, 59, and 68. *The β coefficients can be interpreted as differences in various metabolic risks comparing women with different categories of HPV (human papillomavirus) genotypes to those with negative HPV. †Adjusted for age, race, health behaviors (smoking and alcohol consumption), and sex behavior.

CVD comparing women with presence of vaginal HPV DNA to those without was 2.46 (95% confidence interval [CI]: 1.42 to 4.27). Further covariates adjustment, including health/sex behaviors, medical comorbidities, composite metabolic *z*-score, and cardiovascular risk factors and management (Models 2 to 5), only mildly attenuated the association between HPV and CVD (Table 3). We then examined the relation of HPV genotypes with CVD and found that cancer-associated HPV types were specifically associated with either myocardial infarction or stroke. After controlling for demographics, health/sex behaviors, medical comorbidities, and cardiovascular risk factors and management, the OR of CVD comparing women with cancer-associated HPV types to those with negative HPV was 2.86 (95% CI: 1.43 to 5.70). Presence of other types of HPV DNA was not associated with CVD in the multivariate Models 2 to 5. Interactive effects between age and HPV genotypes on CVD were tested across Models 1 to 5, and no interaction was identified.

Discussion

Among U.S. women age 20 to 59 years, HPV infection is likely associated with myocardial infarction or stroke. Cancer-associated HPV genotypes, but not other HPV genotypes, are selectively related to presence of CVD. The association between HPV and CVD still perseveres after adjustment for health/sex behaviors, medical conditions, and cardiovascular risk burden and management, indicating that conventional risk factors cannot fully explain the relation of HPV to CVD and that presence of HPV infection, especially cancer-associated genotypes, is a strong and independent correlate for CVD. To the best of our knowledge, there is no previous report on the association between HPV and CVD. This is the first report to investigate the association between HPV infection and CVD by using a geographically dispersed and ethnically diverse representative sample of community-dwelling women living in the United States. Potential confounders were also comprehensively considered.

The possible mechanistic explanations behind the newly found association are intriguing. The products of 2 tumor suppressor genes, p53 and retinoblastoma protein (pRb), might be involved in the mechanisms for the association between HPV and CVD. HPV oncoproteins interact with and inactivate both p53 and the pRb. In animal studies using different models, knockout of *p53* gene (12), transplanting mice with bone marrow from *p53* knockout mice (21), and macrophage-specific loss of *p53* function (22) were all associated with considerably increased atherosclerotic lesion size with the presence of more lesion necrosis (21), decreased apoptotic activity (21), and extensive cellular proliferation (12,22) in the atherosclerotic lesions. Retinoblastoma gene, the first tumor suppressor gene identified molecularly, also plays a pivotal role in regulating cell proliferation. In fact, introduction of the *Rb* gene via an adenovirus vector has been shown to inhibit vascular smooth muscle cell proliferation (23). One animal study showed retinoblastoma gene–deleted mice had enhanced atherosclerosis development, involving increases in atherosclerotic lesion area and increases in smooth muscle cell area (24).

Table 3 Association Between Cardiovascular Disease and HPV

	Model 1		Model 2		Model 3		Model 4		Model 5	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Presence of HPV DNA										
Negative (reference)	1.0		1.0		1.0		1.0		1.0	
Positive	2.46 (1.42–4.27)	0.001	2.13 (1.21–3.74)	0.009	2.14 (1.21–3.79)	0.009	2.30 (1.27–4.16)	0.006	2.06 (1.14–3.74)	0.017
HPV genotypes										
Negative HPV (reference)	1.0		1.0		1.0		1.0		1.0	
Other HPV types	2.13 (1.12–4.06)	0.021	1.91 (0.99–3.69)	0.055	1.88 (0.97–3.67)	0.063	1.89 (0.94–3.78)	0.072	1.70 (0.84–3.43)	0.137
Cancer-associated HPV types	2.87 (1.52–5.43)	0.001	2.39 (1.24–4.61)	0.009	2.46 (1.27–4.77)	0.008	2.86 (1.43–5.70)	0.003	2.53 (1.27–5.01)	0.008

Adjusted covariates: Model 1 = Age and race. Model 2 = Model 1 + health behaviors (smoking and alcohol consumption) and sex behavior. Model 3 = Model 2 + medical comorbidities (lung disease, liver disease, thyroid disease, estimated glomerular filtration rate, sexually transmitted disease, history of cervical cancer, history of all other cancer). Model 4 = Model 3 + cardiovascular risk factors and management (hypertension, diabetes mellitus, waist circumference, triglycerides, high-density ipoprotein cholesterol, log-transformed levels of C-reactive protein and urinary albumin-to-creatinine ratio, use of antihypertensive agents or cholesterol-lowering medications). Model 5 = Model 3 +metabolic *z*-score, use of antihypertensive agents or cholesterol-lowering medications. Cancer-associated HPV (human papillomavirus) types = HPV types 16, 18, 31, 33, 35, 39, 45 51, 52, 56, 58, 59, and 68.

CI = confidence interval; OR = odds ratio.

Taken together, HPV oncoproteins inactivate tumor suppressor gene products (p53 and pRb) and may therefore accelerate the atherosclerotic process.

Our study has several implications and also raises a number of important questions for future research. In addition to being a causative pathogen for cervical cancer, HPV appears to have roles in the management and prevention of CVD among women. Detecting the presence of a HPV infection may be useful in identifying and targeting women at risk for subsequent CVD who may require additional attention to avoid the development of cardiovascular events. Second, our findings may serve as a theoretical basis for additional benefit in cardiovascular health with HPV vaccination for women. Bivalent HPV vaccine (HPV2, Cervarix), directed against 2 oncogenic types, HPV 16 and 18, and quadrivalent HPV vaccine (HPV4, Gardasil), directed against 2 oncogenic types, HPV 16 and 18, as well as 2 nononcogenic types, HPV 6 and 11, are the current vaccines to prevent HPV infection and related STDs and tumors. Although HPV 16 and 18 are the only 2 cancer-associated oncogenic vaccine types, efficacy of vaccines for protection against cervical lesions due to other nonvaccine oncogenic types (HPV 31, 33, 35, 39, 45 51, 52, 56, 58, 59, 66, and 68) was demonstrated and estimated to be 37.4% (25). Therefore, HPV vaccination may have potential cardiovascular benefits and could have public health implications. Third, our analysis indicates that infection with cancer-associated HPVs (HPV 16, 18, and nonvaccine oncogenic types) has a strong association with CVD. Data from the previous randomized controlled clinical trials (26,27) of HPV vaccines could be reassessed for cardiovascular endpoints. A clinical study prospectively testing whether HPV immunization positively modifies the cardiovascular outcomes in women may be warranted. An important step towards reducing the disabling impact of CVD is early identification of (and potential interventions for) potential risk factors. Examining these questions may provide evidence of potentially modifiable factors in the setting of CVD prevention. Last, studies for the interaction between HPV oncoproteins and p53/pRb has been mostly confined to HPV types 16 and 18; data from other oncogenic HPV types were sparse (28,29) and are warranted for better understanding of the molecular pathway from HPV infection to atherosclerosis.

Study limitations. The study is cross-sectional, and a causal relationship of HPV infection in the development of cardiovascular events cannot be established and should be further explored. A follow-up study with collection of cardiovascular outcomes in relation to status of HPV infection is required. Second, our analysis was limited to women. The association between HPV and CVD is still unknown among men. Third, although evidence has shown a high correlation of HPV DNA detection in self-collected swabs compared with swabs collected by healthcare professionals (30,31), self-collected cervicovaginal samples, to some extent, may still suffer from under-recognizing HPV infection, thus potentially underestimating the association. Last, determination of cardiovascular events or illness is from self-reporting in the NHANES and may not be able to fully reflect CVD and may suffer from recall bias or misclassification. A proper follow-up with objective confirmation of cardiovascular outcomes is essential. Although the agreement between self-reported cardiovascular endpoints (including myocardial infarction, stroke, pulmonary embolism, and venous thrombosis) with review by study physicians at clinical centers was substantial according to a recent study from the Women's Health Initiatives Study (32), the association between HPV infection and cardiovascular outcome would be more consolidated if cardiovascular variables could be obtained more objectively in the future. Taken together, our findings are hypothesis generating, and the results bring to light several important research questions (such as prospective data collection of objective cardiovascular outcomes in relation to HPV infection, examination of cardiovascular effects from HPV vaccination in existing vaccine trials, or even assessment of atherosclerosis in papillomavirus animal models) that deserve further investigation.

Conclusions

HPV infection, especially cancer-associated oncogenic types, is likely associated with myocardial infarction or stroke among women. The association cannot be explained by coexisting medical conditions, cardiovascular risk factors, metabolic burden, and their management. We provided new information and possible implications on the associations between HPV infection and cardiovascular events among women in the United States where data currently do not exist.

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